

**REMARKS/ARGUMENTS**

**I. SUMMARY**

In response to the Examiner's rejections of claims 39-60 under 35 U.S.C. §112, second paragraph, in the Office Action of November 18, 2004, claims 39 and 40 have been amended. In response to the Examiner's rejections of claims 39-60 under 35 U.S.C. §103(a), Applicants present arguments to distinguish the present claims over the references upon which the Examiner relies in making her rejections. In view of the claim amendments and the arguments presented, withdrawal of the outstanding rejections is earnestly solicited.

**II. THE CLAIMED INVENTION**

The presently claimed invention relates to methods of separating at least one target component, *e.g.*, cells, from a biological sample. The method comprises (1) placing the sample in a separation container, (2) centrifuging the separation container containing the biological sample; and (3) aspirating the target component(s) from the separation container. The separation container contains at least two distinct sets of selection beads and a focusing device with at least one axial bore passage, through which the biological sample can flow while the separation container is being centrifuged. The focusing device is designed such that the density of the focusing device matches, or is substantially equal to, the density of the target component(s) when the target components are bound to the first set of selection beads. Thus, after centrifugation of the sample in the separation container, the first set of selection beads, bound to the target components, and the focusing device will be located in approximately the same vertical position within the container. The target components within the biological sample bind to the first set of selection beads *via* an affinity binding agent on the surface of the selection beads. The second set of selection beads has a different affinity binding agent on the surface than the first set of selection beads, and will thus bind components within the biological sample other than the target component. Additionally, the second set of beads has a different density than both the focusing device and the first set of selection beads. Thus, after centrifugation of the sample in the

separation container, the second set of selection beads, possibly bound to components other than the target components, will not be located in approximately the same vertical position as the focusing device.

The methods of the current invention thus provide a four-fold means of selecting for target components, *e.g.*, cells, in a single container and in a single experiment. The first means of selection involves the positive selection of the cells by their ability to bind the affinity binding agent on the first set of selection beads. The second means of selection involves the positive selection of components, based upon their expected densities after binding to the first set of selection beads. The third means of selection involves the negative selection of cells by their ability to bind the affinity binding agent on the second set of selection beads. The fourth selection means involves the negative selection of components within the biological sample, based upon their densities after binding to the second set of selection beads. The methods of the current invention also result in elongating the target component layer, thus making it easier for a technician to extract the target layer without interfering contamination.

The cited references do not teach or suggest combining all the elements of the current invention as set forth above and in the claims. In particular, it should be noted that nowhere in the cited art is there a teaching or even a suggestion of a single process that is a four-fold separation/selection method that also stretches the target layer, making it easier to extract the target layer from the separation container without contaminants. Therefore, the current invention provides methods not currently available in the art, and is useful for quickly and efficiently isolating at least one target component from a biological sample.

### **III. SUPPORT FOR THE CLAIM AMENDMENTS**

Support for the claim amendments presented herein are found throughout the specification. In particular, support can be found in paragraphs 0001, 0031, 0044, 0055, which collectively describe isolating the component(s) from biological samples using two sets of selection beads, where one set will bind to the target of interest and will settle in the axial bore passage of the focusing device upon centrifugation. These passages of the specification also

describe the affinity agent being bound to the surface of the beads. Accordingly, no new matter has been added by way of the accompanying amendments to the claims.

#### **IV. THE OFFICE ACTION OF NOVEMBER 18, 2004**

##### **A. SUMMARY OF THE OFFICE ACTION**

In the Office Action dated November 18, 2004, the Examiner rejected claims 39-60 under 35 U.S.C. §112, second paragraph, and alleged that the rejected claims are indefinite. The Examiner also rejected claims 39-60 under 35 U.S.C. §103(a) as allegedly being obvious in view of a combination of references. Applicants respectfully request that the Examiner carefully consider the following remarks and withdraw the outstanding rejections in favor of allowance.

##### **B. THE REJECTIONS UNDER 35 U.S.C. §112, SECOND PARAGRAPH ARE MOOT OR TRAVERSED**

In the Office Action of November 18, 2004, the Examiner rejected claims 39-60 under 35 U.S.C. §112, second paragraph, as being indefinite. *Prosecution History of U.S. Serial No. 09/756,590, Office Action mailed November 18, 2004, page 4.* Applicants assert that the previously presented claims fully complied with the requirements of 35 U.S.C. §112, second paragraph; however in the interest of expediting prosecution, claims 39 and 40 have been amended to overcome the Examiner's rejections. It is believed that the amendments to claims 39 and 40, as well as the arguments presented herein address and overcome all aspects of the Examiner's rejections under 35 U.S.C. §112, second paragraph. Furthermore, the claim amendments do not narrow the scope of the claims. Withdrawal of all rejections under 35 U.S.C. §112, second paragraph is appropriate and respectfully requested.

##### **1. "Type of Method"**

In the Office Action of November 18, 2004, the Examiner alleged that claim 39 is "vague and indefinite." *Id.* Specifically, the examiner stated that "[i]t is unclear what constitutes the metes and bounds as to the 'type' of method being claimed in the present invention...." *Id.* Applicants assert that claim 39, as previously presented, was clear and specific in that the "type

of method” was defined by the recited elements. In the interest of expediting prosecution, however, Applicants have amended the preamble to specify the “type” of method claimed. Withdrawal of this rejection is earnestly solicited.

**2. “Possessing”**

In the Office Action of November 18, 2004, the Examiner alleged that “the term ‘possessing’ in claim 39 is a relative term, which renders the claim indefinite.” *Id.* Applicants assert that the term “possessing,” as it was used in the previously presented claim, is not a relative term. In the interest of expediting prosecution, however, Applicants have amended the claim to remove the phrase “possessing.” In light of the claim amendments, the Examiner’s rejection is now moot. Withdrawal of this rejection is earnestly solicited.

**3. “Capable of”**

In the Office Action of November 18, 2004, the Examiner alleged that “the term ‘capable of’ in claim 39 is a relative term, which renders the claim indefinite.” *Id. at page 5.* Applicants wish to remind the Examiner that the phrase “capable of” does not *per se* render a claim indefinite. Instead, the phrase “capable of” is a functional term used to describe a structure, and “[t]here is nothing inherently wrong with defining some part of an invention in functional terms...” *Manual of Patent Examining Procedure (MPEP)*, 8<sup>th</sup> Ed., (February 2003) §2173.05(g). *See In re Barr* 444 F.2d 588 (C.C.P.A. 1971) (the limitation “incapable of forming a dye” was deemed definite). Nonetheless, solely to expedite prosecution, the phrase “capable of specifically binding” has been removed. In light of the claim amendments, the Examiner’s rejection is now moot. Withdrawal of this rejection is earnestly solicited.

**4. “Desired” and “Undesired”**

In the Office Action of November 18, 2004, the Examiner alleged that the terms “desired components” and “undesired components” are “vague and indefinite.” *Prosecution History of U.S. Serial No. 09/756,590, Office Action mailed November 18, 2004, page 5.* Applicants assert

that the terms “desired components” and “undesired components” are definite in that one of ordinary skill in the art would recognize and understand what is meant by these terms in the context of a separation and isolation assay. In the interest of expediting prosecution, however, Applicants have amended the claim to remove the phrases “desired components” and “undesired components.” In light of the claim amendments, the Examiner’s rejection is now moot. Withdrawal of this rejection is earnestly solicited.

**5. “Sample” and “Sample Components”**

In the Office Action of November 18, 2004, the Examiner alleged that the terms “sample” and “sample components” lack antecedent basis, because the “sample” is referred to as a “biological sample” in the first instance. *Id. at page 5.* Applicants assert that the use of the term “sample” as an abbreviated form of “biological sample” does not lack antecedent basis. Furthermore, the term “said sample” is clear because there are no other samples, besides the first “biological sample” mentioned in the claims. Nonetheless, solely to expedite prosecution, Applicants have amended the claim to recite “biological sample” and “biological sample components.” Withdrawal of this rejection is earnestly solicited.

**6. “Being capable of elongating layers”**

In the Office Action of November 18, 2004, the Examiner alleged that the phrase “capable of elongating layers” is “vague and indefinite because it is unclear whether the ‘focusing device’ has the ‘ability’ to ‘elongate’ layers of sample.” *Id. at page 5.* Applicants assert that the claim, as it previously stood, made it clear to one of ordinary skill that the focusing device would elongate layers after the sample was centrifuged in the sample container. In the interest of expediting prosecution, however, Applicants have amended the claims to remove the phrase “being capable of elongating layers.” In light of the claim amendments, the Examiner’s rejection is now moot. Withdrawal of this rejection is earnestly solicited.

**7. “Elongating layers”**

In the Office Action of November 18, 2004, the Examiner alleged that “step (a) and (b) of claim 39 is confusing regard [*sic*] the type of ‘elongating layers’ of the focusing device.” *Id. at page 6*. Applicants assert that the term “sample layer” is readily understood by one of ordinary skill in the art, thus the phrase “elongating layers” would also be readily understood. In the interest of expediting prosecution, however, the phrase “elongating layers” has been removed. In light of the claim amendments, the Examiner’s rejection is now moot. Withdrawal of this rejection is earnestly solicited.

**8. “Target”**

In the Office Action of November 18, 2004, the Examiner alleged that the term “target” lacked antecedent basis and was also “vague and indefinite because it is unclear whether it is referring to the ‘desired component’ or the ‘undesired component.’” *Id. at page 6*. Applicants assert that using the term “target” for the first time in (b) of claim 39 does not render the claim indefinite for lack of antecedent basis. Indeed, “the failure to provide explicit antecedent basis for terms does not always render a claim indefinite.” *MPEP*, 8<sup>th</sup> Ed. (February 2003) §2173.05(e). Applicants further assert that the scope of claim, as it previously stood, was “reasonably ascertainable by those skilled in the art” and thus complied with the requirements of 35 U.S.C. §112, second paragraph. *Id. (citing Ex Parte Porter*, 25 U.S.P.Q.2d 1144 (Bd. Pat. App. & Inter. 1992)). Solely to expedite prosecution, however, Applicants have amended claim 39 to recite the phrase “target component” prior to (b).

Applicants also assert that the term “target” was not unclear in that one of skill in the art would have readily understood the scope and meaning of the term “target” when used as it was in the previously presented claim. Again, Applicants have amended and removed the terms “desired” and “undesired” in claim 39 to expedite prosecution. Withdrawal of both rejections involving the term “target” is earnestly solicited.

**9. “Substantially Absent”**

In the Office Action dated November 18, 2004, the Examiner rejected claim 39 because “[t]he phrase ‘substantially absent’ in claim 39 is considered indefinite because it is unclear as to the means of measuring the degree of ‘substantially’ ....” *Prosecution History of U.S. Serial No. 09/756,590, Office Action mailed November 18, 2004, page 6*. Applicants assert that the phrase “substantially absent” does not render the claim indefinite. Rather, the claims “read in light of the specification[], reasonably apprise those of skill in the art both to the utilization and scope of the invention....” *Shatterproof Glass Corp. v. Libbey-Owens Ford Co.* 758 F.2d 613, 624 (Fed. Cir. 1985) (quoting *Georgia-Pacific Corp. v. United States Plywood Corp.* 258 F.2d 124, 136 (2d Cir. 1958)). Indeed, the specification makes it clear that the methods of the invention are designed to significantly enrich samples for target components “compared to many prior processes and have a substantially lower contaminant level of [contaminants]” *U.S. Application Serial No. 09/756,590, paragraph 0050*. Thus the specification provides guidance, and the claim terms are as “precise as the subject matter permits.” *Shatterproof Glass*, 758 F.2d at 624.

Furthermore, the Examiner is reminded that “[s]ome latitude in the manner of expression and the aptness of terms should be permitted even though the claim language is not as precise as the examiner might desire.” *MPEP*, 8<sup>th</sup> Ed. §2173.02. In view of the foregoing arguments, withdrawal of this rejection is earnestly solicited.

**C. THE REJECTIONS UNDER 35 U.S.C. §103 ARE TRAVERSED**

In the Office Action of November 18, 2004, the Examiner rejected claims 39-60 as allegedly being unpatentable over U.S. Patent No. 5,776,710 (“Levine ‘710”) and U.S. Patent No. 5,393,674 (“Levine ‘674”). In view of the specification of Levine ‘710 being identical to the specification of U.S. Patent No. 5,635,362, already of record, Applicants reiterate and incorporate by reference arguments previously set forth during prosecution of the current application. Applicants also submit the following additional remarks. For the reasons set forth below, Applicants assert that the currently claimed invention is not obvious over the cited

references, alone or in combination. Withdrawal of the obviousness rejection is earnestly solicited.

**1. The Differences Between the Cited Art and the Currently Claimed Invention**

*a) Levine '710*

In alleging that claims 39-60 are obvious under 35 U.S.C. §103, the Examiner states that “Levine ‘710 discloses the method for *detecting* a target analyte in a biological sample....” *Prosecution History of U.S. Serial No. 09/756,590, Office Action mailed November 18, 2004, page 7* (emphasis added). The Examiner also states that “[t]he method of Levine ‘710 differs from the presently claimed invention by failing to include the step of removing the desired component....” *Id. at page 8*. Applicants respectfully disagree with this interpretation of Levine ‘710. Namely, the methods of Levine ‘710 result in the analyte being trapped, or sandwiched, and affixed to the surface of a tube insert. For example, Levine ‘710 states that “the analyte-capture binding material [is] coated ... on the float insert.” *United States Patent No. 5,776,710, col. 7, ll. 36-38*. The relationship between the position of the analyte-binding material and the target analyte is very different between Levine ‘710 and the currently claimed invention. That the analyte-binding material is affixed to a solid surface is at least one reason why Levine ‘710 fails to teach or even suggest removal of the analyte. Indeed, the methods of Levine ‘710 render the analyte affixed to a solid surface and, consequently, immobile and thus completely unavailable for removal. Indeed, the specification of Levine ‘710 discusses the analyte as being “captured” and refers to the analyte binding material as the “analyte-*capture* binding material.” *United States Patent No. 5,776,710, col. 7, ll. 3-13; col. 7, ll. 36-37*. In fact, it is because of these differences in mobility of the target analyte that one of skill in the art would not be able to modify the methods of Levine ‘710 to arrive at the claimed invention. Indeed, modifying Levine ‘710 to render the analyte-capture material mobile would render Levine ‘710 totally inoperable, as the analyte would not longer be affixed to specific portions of the inserts.



In addition, this “sandwiching” aspect of analyte capture disclosed in Levine ‘710 also requires, by its very nature, *two* separate binding events to properly *capture* the analyte. *See U.S. Patent No. 5,776,710*, col. 8, ll. 42-55 (discussing the need for two binding events for proper capture and subsequent detection). In essence, the methods of Levine ‘710 are simply an ELISA sandwich assay within a tube, as compared to a 96-well plate. In contrast, the methods of the currently claimed invention only *require* one binding event and thus do not remotely resemble an ELISA sandwich assay. The target analytes of the currently claimed invention are, in fact, not captured in an antibody-analyte-particle sandwich. Rather, the methods of the currently claimed invention require that the target analytes and/or the analyte-microbead complexes are freely mobile at all times and not sandwiched. In fact this lack of sandwiching in the currently claimed invention provides for the mobility of the analyte-microbead complexes, allowing the target analytes to be aspirated after centrifugation.

b) *Levine ‘674*

In alleging that claims 39-60 are obvious under 35 U.S.C. §103, the Examiner states that “Levine ‘674 disclose a method for harvesting target cells from a centrifuged sample of blood ....” *Prosecution History of U.S. Serial No. 09/756,590, Office Action mailed November 18, 2004, page 8*. The differences between the methods of the currently claimed invention and Levine ‘674 are so great as to render Levine ‘674 irrelevant. Indeed, Levine ‘674 does not teach, mention or even suggest that microbeads or particulate carriers be used in conjunction with the float. Thus, the methods of Levine ‘674 provide, at most, a density selection method for isolating target components from a biological sample. Practicing the methods of Levine ‘674 results in isolating components, including contaminants, from a biological sample, where the isolated components have similar densities. In contrast to Levine ‘674, and as discussed previously herein, the methods of the currently claimed invention provide at least a 4-fold selection means for isolating target components from a sample, based on densities and binding affinities. As a result, the methods of the currently claimed invention result in a much richer cell harvest with substantially lower levels of contaminants.

**2. The Currently Claimed Invention is not *Prima Facie* Obvious**

The Examiner states that “[i]t would have been obvious ... to include the step of removing the desired component ... as taught by Levine ‘674 in the method of Levine ‘710.” *Prosecution History of U.S. Serial No. 09/756,590, Office Action mailed November 18, 2004, page 9*. Applicants respectfully submit that there is no motivation in the references to combine them, and respectfully disagree with this assertion that the combination of Levine ‘710 and Levine ‘674 would render the currently claimed invention obvious.

To establish a case of *prima facie* obviousness, the Examiner must meet three criteria. First, the Examiner must show that the references upon which she or he relied teach *every* limitation of the currently claimed invention, *In re Royka* 490 F.2d 981, 985 (C.C.P.A. 1974). Second, the Examiner must show that there is some suggestion or motivation in the references themselves, or within the knowledge of one of ordinary skill in the art, to combine the references to arrive at the claimed invention. Lastly, the Examiner must show that there is a reasonable expectation of success in combining the references, and that this expectation of success is found in the references as well. *In re Vaeck* 947 F.2d 488, 493 (Fed. Cir. 1991). Applicants assert that the cited art, alone or in combination, does not teach each and every limitation of the currently claimed invention, nor do the references provide any teaching, suggestion or motivation to combine the cited art to arrive at the claimed invention, with a reasonable expectation of success.

From the previous discussions of the differences between the currently claimed invention and the cited art, it should be readily apparent that the cited art does not and cannot teach each and every element of the currently claimed invention. Indeed, neither Levine ‘710 nor Levine ‘674, alone or in combination, teaches a method comprising the use of a float with an axial bore passage *and* microbeads that bind the target component.

Additionally, nowhere in the prior art is there a suggestion or motivation to combine Levine ‘710 and Levine ‘674 to arrive at the currently claimed invention. Indeed, one of skill in the art, reading Levine ‘710, could not look to Levine ‘674 to provide a removal step to the methods disclosed in Levine ‘710. As discussed herein, the methods of Levine ‘710 render the

target analytes immobile and completely incapable of removal. Furthermore, modifying the methods of Levine '710, in an attempt to render the captured analyte more mobile and thus amenable to removal, would destroy the operability of Levine '710. Thus, there would be no motivation to combine the cited references, because the methods disclosed in the cited references can *not* be combined while still retaining their functionality. Furthermore, because the cited art does not contain any motivation to combine the cited references, the prior art can not possibly convey a reasonable expectation of success in combining the references to arrive at the claimed invention. And "[b]oth the suggestion [to carry out the claimed process] and the expectation of success must be founded in the prior art, ...." *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988). In contrast to a reasonable expectation of success, one of skill in the art would understand that the cited art could not be combined with any degree of success.

Neither Levine '710 nor Levine '674, alone or in combination, teaches each and every element of the claimed invention. In addition, one of skill in the art would, recognizing that the references could not be combined while still retaining operability, would never be motivated to combine Levine '710 and Levine '674 to arrive at the currently claimed invention. Finally, because Levine '710 and Levine '674 could not be combined in any operable means, one of skill in the art could not have a reasonable expectation of success in producing the currently claimed invention. Accordingly, Applicants assert that the cited references fail to render the currently claimed invention obvious under 35 U.S.C. §103. Reconsideration and withdrawal of this rejection is earnestly solicited.

**V. CONCLUSION**

In response to the Office Action of November 18, 2004, Applicants have amended claims 39, 40 and 60 herein. Claim 60 has been amended to correct a typographical error. In view of the amendments to the claims and the arguments presented, reconsideration and withdrawal of the outstanding rejections is earnestly solicited.

Should the Examiner believe that further discussion of any remaining issues would advance the prosecution, she is invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,

Date

February 16, 2005

By

Todd B. Buck

Castellano Malm Ferrario & Buck PLLC

Customer Number: 46851

Telephone: (202) 478-5300

Facsimile: (202) 318-1288

Todd B. Buck

Registration No. 48,574